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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,692	01/25/2001	Anne Charlotte Arentsen	6124.200-US	5360

23650 7590 05/20/2004

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,692	ARENTSEN, ANNE CHARLOTTE	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDMENT OF THE AMENDMENT, REMARKS AND THE STATUSOF THE CLAIMS

1. The amendment and remarks filed 2/27/04 are acknowledged, entered and considered. In view of Applicant's request, claims 1-15 have been canceled and claims 16-52 have been added. Claims 16-52 are now pending in the application.

The objection to the specification and the rejections under 35 U.S.C. 112, second paragraph, 35 U.S.C. 102(b) and 35 U.S.C. 103(a) over the prior art of record are withdrawn in view of Applicant's amendment, remarks and cancellation of the claims. Applicant's amendment, remarks and cancellation of claims with respect to the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) over the prior art of record have been considered but deemed to be moot in view of the new ground of rejections necessitated by Applicant's amendment.

NEW GROUNDS OF REJECTION

CLAIMS REJECTION-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/30731 taken with EP 0 619 322 and WO 98/08871.

WO 99/30731 teaches a process for producing crystals of GLP-1 analog which involves preparing an aqueous solution comprising a GLP-1 analog at temperature of 15-37^{0}C, preferably about 18-25^{0}C (i.e. overlaps with the limitations of 20-25^{0}C of claims 16 and 26) for a time sufficient to allow production of the crystals, wherein said aqueous solution has a pH from about 6 to 7 (i.e., meets the limitations of claims 16 and 26), preferably about 6.4 ± 0.2 (i.e., meets the limitations of claims 23, 24, 35 and 36) and comprises in addition of 0-200 mM of inorganic salt which is NaCl, preferably 0-150 mM NaCl (i.e., overlaps with the limitations of claims 16, 22, 25, 26, 34 and 37 which is 100-200 mM) and from about 2-15% (v/v), preferably 3-13% (v/v) ethanol (i.e., overlaps with 1-15%, or 5-10% (vol/vol) ethanol of claims 16, 18, 26, and 30, respectively). See e.g., page 11, lines 4-17, and page 12, lines 9-21 as directed to claims 16, 18, 22-26, 30 and 34-37. Also, the reference discloses on page 11, lines 8-9 that the crystallization solution contains a GLP concentration of about 1-10 mg/ml, preferably 2-7 mg/ml; and on page 12, lines 5-6, the GLP concentration is in the range of approximately 1-20 mg/ml, preferably about 2-10 mg/ml, and as such overlaps with the ranges of 2-10 mg/ml as claimed in claims 17 and 29. On page 11, lines 10-13, the reference states that a number of conventional buffer solutions are suitable in the practice of the invention. 10 to 50 mM Bis-Tris buffer is preferred, thus, meeting the limitations of claims 19-21 and 31-33, which are directed to Bis-Tris buffer having a concentration between 5-10 mM.

The primary reference of WO 99/30731 on page 5, defines "GLP-1 analog" as a molecule having one or more amino acid substitution, deletions, inversions, or additions relative to GLP-1 (7-37). On page 6, lines 8-15 shows the substitution of various amino acids at different position including arginine at position 34. On page 7, lines 11 to page 8, lines 2, the reference further defines a "GLP-1 derivative" as a molecule having the amino acid sequence of GLP-1 (7-37) or of a GLP-1 analog, but additionally having chemical modification of one or more of its amino acid side groups, α-carbon atoms, terminal amino groups, or terminal carboxylic acid group. Modification at amino acid side groups include, without limitation acylation of lysine ε-amino groups, N-alkylation of arginine, histidine, or lysine, etc. and concludes by stating that one or more side groups, or terminal groups, may be protected by protective groups known to the ordinary-skilled protein chemist, and as such meet the limitation of a method for producing an acylated GLP-1 analogue as recited in claim 26. On page 9, lines 12 to 16, the primary reference defines "Biosynthetic GLP-1 analogs" as any GLP-1 analogs or derivatives [may include Arg^{34}GLP-1 (7-37)] which contain only naturally occurring amino acid residues and are thus capable of being expressed by living cells, including recombinant cells and organisms. Further, on page 10, lines 15 to 21, the reference states that the state of the art of molecular biology provides the ordinary skilled artisan another means by which GLP's can be obtained. Although GLP's may be produced by solid phase peptide synthesis, recombinant methods, or by fragment glucagons, recombinant methods are preferable when producing biosynthetic GLP's analogs because higher yields are possible and as such meets the limitations of claim 27. Thus, in view of the

above, the primary reference clearly teaches the method for producing an acylated GLP-1 analogue, or the production of GLP-1 analog recombinantly which may include Arg^{34} GLP-1 (7-37).

WO 99/30731 differs from claims 16-37 in not teaching the method of producing needle shaped crystals of GLP-1 analogs , wherein the GLP-1 analog is Arg^{34} GLP-1 (7-37). However, the secondary reference of EP 0 619 322 clearly discloses the process of making needle shaped crystals of a GLP-1 analog and product thereof. Although, as discussed above, the primary reference of WO 99/30731 on page 5, defines "GLP-1 analog" as a molecule having one or more amino acid substitution, deletions, inversions, or additions relative to GLP-1 (7-37). On page 6, lines 8-15 shows the substitution of various amino acids at different position including arginine at position 34. Nevertheless, the reference of WO 98/08871 discloses method for producing GLP-1 analog wherein the GLP-1 analog is Arg^{34} GLP-1 (7-37). See e.g. page 17, lines 33 to pages 30, lines 6.

Therefore, in view of the above, one of ordinary skill in the art would have been motivated at the time the invention was made to adapt the conventional secondary references teachings of using needle shaped crystals of GLP-1 and wherein the GLP-1 analog is Arg^{34} GLP-1 (7-37) into the method of the primary reference of WO 99/30731 because including such features into the method of WO 99/30731 reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages for producing needle-shaped crystals of GLP-1 analog or an acylated GLP-1 analog, wherein the GLP-1 analog is Arg^{34} GLP-1 (7-37), which involves

preparing an aqueous solution comprising a GLP-1 analog, a salt, a buffer, and an organic solvent at a temperature of between 20-25^{0}C for a time sufficient to allow production of said crystals, wherein said aqueous solution has a pH 6 to 7. Therefore, the combined teachings of the prior art makes obvious a method for producing crystals of GLP-1 analogs, such as needle-shaped crystals or an acylated GLP-1 analog which was recombinantly expressed thereof, absence of sufficient objective factual evidence or unexpected results to the contrary.

APPLICANT'S ARGUMENTS ARE UNPERSUASIVE

3. Applicant has argued that claims 16-37, the two pending independent claims 16 and 26 are directed to crystallization of a specific GLP-1 analogue [Arg^{34} GLP-1 (7-37)] to produce needle-shaped crystals under specific conditions (100-200 mM inorganic salt, 1-15% ethanol and 20-25^{0}C) that are neither taught nor suggested by the combination of the cited art is unpersuasive. It is noted that Applicant has canceled method claims 1-15 and added new claims 16-52. The combined teachings of the prior art as discussed above, clearly teach the production of needle-shaped crystals of GLP-1 analog or an acylated GLP-1 analog, wherein the GLP-1 analog is Arg^{34} GLP-1 (7-37) under specific conditions (100-200 mM inorganic salt, 1-15% ethanol and 20-25^{0}C).

With respect to Applicant's argument that the production of regular shaped needle shaped crystals of Arg^{34} GLP-1 (7-37) as observed when ethanol was used as the solvent but that the production of needle shaped crystals of Arg^{34} GLP-1 (7-37) was not observed when glycerol was used as a solvent is the result that is neither taught nor

suggested by the prior art is unpersuasive. Contrary to Applicant's argument, the claims were not rejected in the previous Office action or now on the limitations of "using glycerol" as argued by Applicant. Rather, the claims were previously rejected on the limitations of "organic solvent" and now as amended on the limitations of "ethanol". Thus, Applicant's argument is directed to the limitations that are not recited in the claims. Further, Applicant asserts that the additional limitations contained in dependent claims 17-25 and 27-37 further distinguish the claimed method from the combined teachings of the prior art is unpersuasive. The prior art as discussed above clearly teaches the additional limitations contained in dependent claims 17-25 and 27-37, and as such the limitations recited in claims 17-25 and 27-37 will not distinguish the claimed method from the combined teachings of the prior art as asserted by Applicant.

In regard to claims 38-52, Applicant has argued that none of the references cited by the Examiner teaches or suggest the crystallization of exendin-4 is noted. However, this argument is rendered moot because claims 38-52 are not rejected under 35 U.S.C. 103(a) over the prior art of record as argued by Applicant.

CLAIMS REJECTION-35 U.S.C. 112, 1st PARAGRAPH

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no description in the instant specification for the claimed method of producing crystals of **exendin-4**, said method comprising an aqueous solution of said exendin-4 at a temperature of between 4-37^{0}C for a time sufficient to allow production of said crystals, wherein said aqueous solution has a pH of pI<pH<pI + 2 and comprises in addition to said exendin-4, at least 25 mM of a salt and at least 0.5% (vol/vol) organic solvent as claimed in independent claim 38 and the additional limitations contained in dependent claims 39-52. It is noted as stated by Applicant on page 7 of the remarks filed 2/27/04 that added claims 38-52 find support inter alia at page 2, line 28, page 3, lines 16-17, page 13, lines 2-31, page 14, lines 4-5, and page 18, line 26 of the specification. However, none of the cited pages above in the instant specification support the crystallization of exendin-4 in the manner claimed in claims 38-52. Page 2, line 28 states that in step a) a buffer may be optionally be added to said solution (i.e., referring to the solution comprising GLP-1 analog and not to a solution comprising exendi-4). On page 3, lines 16-17, the specification discloses the adjustment of pHs for GLP-1 analogs and not for exendrin-4 as alleged by Applicant. On page13, lines 2-31, the specification discloses various salts and organic solvents with their respective concentrations to be used in GLP-1 solution and not in exendrin-4 solution as asserted by Applicant. Similarly, on page 14, lines 4-5, the

specification discloses various ranges of temperatures to be used in GLP-1 solution and not in exendin-4. On page 18, line 26 of the specification defines the term "exendins" and not the crystallization of exendin-4 in the manner claimed in claims 38-52. Thus, the scope of the currently presented claims 38-52 is not supported in the instant specification.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 16-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 16 is indefinite in the recitation of "1-15% (w/w) ethanol" because it is inconsistent with claims 18, 26 and 30, which recite the percentages of the ethanol in (vol/vol), rather than in (w/w). Appropriate correction is required.

ACTION IS FINAL, NECESSITATED BY AMENDMENT

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

CONCLUSION AND FUTURE CORRESPONDENCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

AAMohamed/AAM

5/14/04